Detailed comparison of the safety of tivozanib hydrochloride versus sorafenib in patients with advanced/metastatic renal cell carcinoma (mRCC) from a Phase III trial

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Introduction

- Tyrosine kinase inhibitors such as sorafenib and sunitinib inhibit multiple tyrosine kinases that may lead to off-target toxicities, such as palmar–plantar erythrodysesthesia syndrome or diarrhea[1–3]
- Tivozanib hydrochloride (tivozanib) is a highly potent, selective, and long half-life (4.5–5.1 days) tyrosine kinase inhibitor targeting all three vascular endothelial growth factor receptors (VEGFRs 1, 2, and 3)[4–7]
  - This high level of selectivity is expected to lead to a lower level of off-target toxicities[4,5]
- A Phase III trial (TIVO-1) comparing tivozanib 1.5 mg once daily (for 3 weeks on/1 week off) versus sorafenib 400 mg twice daily (continuously) in a 4-week cycle in patients with mRCC showed significant improvement in progression-free survival for tivozanib compared with sorafenib. A favorable safety profile with a low incidence of off-target adverse events (AEs) and low frequency of dose reductions and interruptions was observed for tivozanib in this study[8]
- Here we discuss detailed drug-related AE data from this Phase III trial with the goal of providing a better understanding of the tivozanib safety profile

Objective

- To compare the safety and tolerability of tivozanib and sorafenib in patients with mRCC

Methods

Study Design

- TIVO-1 was an open-label, randomized, controlled, multinational, multicenter, parallel-arm study comparing tivozanib with sorafenib in patients with mRCC (clear-cell component) who had a prior nephrectomy and who had received ≤1 prior systemic treatment (immunotherapy, including interferon-alfa or interleukin-2–based therapy; chemotherapy; or hormonal therapy) for mRCC. Patients (Eastern Cooperative Oncology Group [ECOG] performance status ≤1) were randomized (1:1) to tivozanib 1.5 mg once daily for 3 weeks followed by a 1-week rest, or sorafenib 400 mg twice daily continuously in a 4-week cycle
- Patients with prior vascular endothelial growth factor–targeted therapy or mammalian target of rapamycin–targeted therapy, or with significant cardiovascular disease within 6 months of the first dose of study drug, were excluded

Safety Assessments

- Safety assessments included AEs, vital signs, physical examination, ECOG performance status scores, electrocardiograms (ECGs), and laboratory results
  - AEs were recorded from Day 1 until 30 days after last dose of study drug. AE relationship to study drug was assessed by the investigator
  - Blood pressure (mmHg) was measured after a 5-minute rest period on Days 1 and 15 of Cycle 1, on Day 1 of subsequent cycles (end-of-treatment visit), and at the 30-day follow-up visit

Analysis

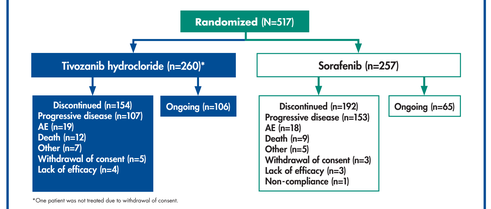
- Descriptive statistics of drug-related AEs are presented
- The percentages of patients who discontinued study drug and time to discontinuation, along with reasons for discontinuation, were summarized for the intent-to-treat population (defined as all randomized patients)
- The safety population was defined as all randomized patients who received at least one dose of either study drug. For the safety population, treatment group was designated according to the actual study treatment received. This population was used for all safety analyses

Results

Patients' Disposition and Demographics

- Of the 517 randomized patients, 346 discontinued, and 171 were on study, as of December 2011 **(Figure 1)**
- The most common reason for study drug discontinuation was progressive disease (69.5% of discontinuations in the tivozanib group and 79.7% in the sorafenib group)
- The time to study drug discontinuation was significantly longer for the tivozanib group compared with sorafenib (median time of 12.3 vs 9.5 months, respectively) (P=0.002). The percentage of patients who discontinued due to drug-related AEs was similar (4.2% in the tivozanib group vs 5.4% in the sorafenib group)
- Baseline demographic characteristics were similar between the treatment groups, with the exception of ECOG performance status, which favored the sorafenib arm **(Table 1)**. Median age for both treatment groups was 59.0 years, with a range of 23–85 years. Patients were predominantly from Central/Eastern Europe, and approximately 70% were male

Figure 1. Patient disposition.



AE, adverse event.

Table 1. Baseline Characteristics

Characteristic	Tivozanib (n=260)	Sorafenib (n=257)
Gender, n (%)		
Male	185 (71.2)	189 (73.5)
Female	75 (28.8)	68 (26.5)
Age, years		
Mean (range)	58.2 (23–83)	58.4 (23–85)
Geographic Region[a], n (%)		
Central/Eastern Europe	229 (88.1)	228 (88.7)
North America/Western Europe	22 (8.5)	18 (7.0)
Rest of World	9 (3.5)	11 (4.3)
ECOG performance status[b], n (%)		
0	116 (44.6)	139 (54.1)
1	144 (55.4)	118 (45.9)

ECOG, Eastern Cooperative Oncology Group.
[a]Geographic region was a randomization stratification factor. [b]Imbalance between arms. P<0.05 by Fisher exact test.

Safety

Exposure

- Relative dose intensity (actual dose administered divided by the assigned dose for the time the patient was on study) was 94.32% for tivozanib patients and 81.25% for sorafenib patients

Adverse Events

- Drug-related AEs occurred in fewer patients on tivozanib than patients on sorafenib (67.6% vs 83.3%). The most common drug-related AEs (≥5% in either group) are shown in **Table 2**
- Hypertension, dysphonia, and diarrhea were the most frequent tivozanib-related AEs. Palmar–plantar erythrodysesthesia syndrome, hypertension and diarrhea were the most frequent sorafenib-related AEs
- Fewer patients in the tivozanib group had ≥Grade 3 drug-related AEs than patients in the sorafenib group (36.3% vs 51.0%, respectively). Drug-related AEs ≥Grade 3 occurring in ≥2.0% of patients are summarized in **Table 3**. ≥Grade 3 hypertension was more common in the tivozanib group, and ≥Grade 3 palmar-plantar erythrodysesthesia syndrome, diarrhea and lipase elevation were more common in the sorafenib group

Serious Adverse Events and Deaths

- In the tivozanib group, 17 (6.6%) patients had drug-related serious AEs, compared with 21 (8.2%) in the sorafenib group. The most frequent drug-related SAEs are shown in **Table 4**
- Thirty-one deaths occurred within 30 days of the last dose of study drug; 9 in the tivozanib arm and 4 in the sorafenib arm appeared to have been due to underlying disease progression, whereas 9 in each arm were related to other causes
  - In the tivozanib arm, 2 deaths were due to myocardial infarction, 2 were due to cardiac failure, and 1 each was due to hypertension, dyspnea, cerebrovascular accident, aortic aneurysm rupture, and pulmonary embolism
  - In the sorafenib arm, 3 deaths were due to cerebrovascular accident, 2 were due to cardiac failure, and 1 each was due to coronary artery insufficiency, hemorrhage, pulmonary embolus, and acute respiratory distress syndrome

Table 2. Commonly Reported (≥5% of Patients in Either Group) Drug-related Adverse Events (Safety Population)

	Tivozanib (n=259), n (%)	Sorafenib (n=257), n (%)
Any drug-related AE	175 (67.6)	214 (83.3)
Hypertension	109 (42.1)	79 (30.7)
Diarrhea	47 (18.1)	71 (27.6)
Dysphonia	47 (18.1)	11 (4.3)
Palmar–plantar erythrodysesthesia syndrome	34 (13.1)	137 (53.3)
Fatigue	28 (10.8)	28 (10.9)
Stomatitis	26 (10.0)	19 (7.4)
Asthenia	21 (8.1)	20 (7.8)
Nausea	15 (5.8)	14 (5.4)
Decreased appetite	13 (5.0)	20 (7.8)
Weight decreased	11 (4.2)	22 (8.6)
Alopecia	6 (2.3)	53 (20.6)
Erythema	3 (1.2)	14 (5.4)
Rash erythematous	3 (1.2)	13 (5.1)
Rash papular	1 (0.4)	15 (5.8)

AE, adverse event.

Table 3. Grade ≥3 Drug-related Adverse Events Reported by ≥2% of Patients in Either Group

	Tivozanib (n=259), n (%)	Sorafenib (n=257), n (%)
Any drug-related AE ≥Grade 3	94 (36.3)	131 (51.0)
Hypertension	61 (23.6)	39 (15.2)
Fatigue	7 (2.7)	7 (2.7)
Palmar–plantar erythrodysesthesia syndrome	5 (1.9)	43 (16.7)
Diarrhea	5 (1.9)	15 (5.8)
Lipase increased	2 (0.8)	15 (5.8)

Table 4. Most Common Drug-related Serious Adverse Events

Tivozanib n=259	n (%)
Any drug-related SAE	17 (6.6)
Abdominal pain	2 (0.8)
Hypertension	2 (0.8)
Fatigue	2 (0.8)
Sorafenib n=257	**n (%)**
Any drug-related SAE	21 (8.2)
Anemia	3 (1.2)
Cerebrovascular accident	2 (0.8)
Pleural effusion	2 (0.8)
Epistaxis	2 (0.8)

Dose Interruptions and Reductions

- Dose interruptions due to an AE occurred in 17.8% of tivozanib patients and 35.4% of sorafenib patients (P<0.001 by Fisher exact test)
- Dose reductions due to an AE in tivozanib patients (11.6%) were fewer than in the sorafenib patients (42.8%; P<0.001 by Fisher exact test)

Hypertension

- Hypertension was a frequent drug-related AE in both treatment groups, occurring in 42.1% of tivozanib patients and 30.7% of sorafenib patients. Death as a result of hypertension (associated with suspected overdose of 4.5 mg [3 capsules] of tivozanib in 1 day) occurred in one tivozanib-treated patient, and no patients in the sorafenib group. The incidence and time to first occurrence of combined hypertension is summarized in **Table 5**
  - Hypertension in both groups was managed with standard antihypertensive medication, including beta-blockers and ACE inhibitors

Table 5. Incidence and Time to First Occurrence of Combined Hypertension

	Tivozanib (n=259)	Sorafenib (n=257)
Patients with combined hypertension[a] – n (%)	119 (45.9)	92 (35.8)
Time to start of first combined hypertension AE[b] – weeks		
Mean (STD)	8.2 (11.62)	9.6 (14.85)
Median	2.7	2.3

[a]Combined hypertension AEs include the following preferred terms: hypertension, blood pressure increased, hypertensive crisis, and essential hypertension.
[b]If a patient experienced more than one of these adverse events, the time to the first event is summarized.
AE, adverse event; STD, standard deviation.

- The greatest increase in mean blood pressure tended to occur early in the study (by Cycle 1 Day 15) and resolve after stopping the study drug (tivozanib or sorafenib) **(Table 6)**

Table 6. Blood Pressure Change from Baseline

	Tivozanib n=259	Sorafenib n=257
SYSTOLIC BLOOD PRESSURE (mmHg)		
Cycle 1 Day 15, n	257	255
Mean (STD)	4.4 (11.97)	4.4 (12.80)
Cycle 2 Day 1, n	257	252
Mean (STD)	3.4 (12.62)	4.9 (13.00)
End of treatment, n	120	169
Mean (STD)	0.5 (14.37)	0.8 (15.98)
DIASTOLIC BLOOD PRESSURE (mmHg)		
Cycle 1 Day 15, n	257	255
Mean (STD)	4.6 (9.54)	3.1 (8.18)
Cycle 2 Day 1, n	257	252
Mean (STD)	4.2 (9.39)	3.4 (8.64)
End of treatment, n	120	169
Mean (STD)	1.9 (8.07)	0.6 (11.20)

STD, standard deviation.

Laboratory Evaluations, Vital Signs, and ECOG Performance Status

- Clinical laboratory findings and vital signs were generally similar between the two treatment groups. However, there was a higher incidence of Grade 3/4 liver function test abnormalities and Grade 3/4 hypophosphatemia observed in the sorafenib group compared with the tivozanib group **(Table 7)**
- Twenty-four percent of patients in the tivozanib group and 6% in the sorafenib group had normal thyroid-stimulating hormone (TSH) levels prior to dosing that increased to >10 mIU/L after treatment. Few of these patients had low T3 (tivozanib 3%; sorafenib 2%) or low free T4 (tivozanib 2%; sorafenib <1%) on or after date elevations in TSH were observed
- Compared with values at baseline, ECOG performance status decreased in 31% of patients in the tivozanib group and 34% in the sorafenib group

Table 7. Selected laboratory abnormalities

	Tivozanib (n=259), %		Sorafenib (n=257), %	
	All Grade	Grade 3 (4)	All Grade	Grade 3 (4)
Chemistries				
ALT increase	26	<1	34	3 (<1)
AST increase	34	2	49	3 (<1)
Amylase increase	40	4 (<1)	52	6 (<1)
Lipase increase	45	8 (2)	62	20 (4)
Hypophosphatemia	27	4	70	25
Proteinuria	68	3	72	2
Hematology				
Low hemoglobin	36	2 (2)	46	3 (<1)
Neutropenia	10	2 (<1)	9	1 (<1)
Thrombocytopenia	17	0 (<1)	11	0

Conclusions

- Tivozanib was well tolerated with low rates of off-target AEs and fewer dose reductions and interruptions than sorafenib in patients with mRCC. Patients receiving tivozanib experienced more hypertension and dysphonia, but less diarrhea, palmar–plantar erythrodysesthesia syndrome, and alopecia than patients on sorafenib
- The overall incidences of drug-related AEs and drug-related ≥Grade 3 AEs were lower with tivozanib than with sorafenib
- Although hypertension was common and occurred early (within the first 2–3 weeks) with tivozanib, it was generally managed medically and was rarely a reason for dose reduction, interruption or discontinuations, and there was no evidence of increased cardiovascular consequences with tivozanib, compared with sorafenib
- Given its tolerability profile, tivozanib may present a potential treatment option for patients with advanced renal cell carcinoma

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